Reviewer's report:

Title: A novel deleterious PTEN mutation in a patient with early-onset bilateral breast cancer

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Reviewer: Michel Longy

The paper by Pradella et al, « A novel deleterious PTEN mutation in a patient with early onset bilateral breast cancer » reports the case of a female patient showing clinical features of Cowden disease including bilateral breast cancer. PTEN molecular analysis revealed a disease causing missense mutation which was not able to revert the PI3K/AKT pathway activation in a PTEN null cell model.

The paper does not really add new information except for the pathogenic effect of this specific mutation. This is however a detailed observation with careful and thorough biological investigation of the consequences of a PTEN mutation.

Comments:

The tumour from which PTEN and AKT immunostaining was performed is not specified. It would be interesting to repeat the analysis on the three breast tumours presented by this patient and compare the results.

According to the material available, the same remark could also concern the somatic mutation screen of the PTEN, AKT and PIK3CA genes.

I disagree with the authors when they say that PTEN acts as monoallelic defect in breast cancers occurring in Cowden patients. Literature data are consistent with the Knudson model in this situation (cf Banneau et al. Breast Cancer Res. 2010;12(4):R63). PTEN IHC remains positive in this patient because the missense mutation does not activate the NMD and maintain a protein expression. The absence of LOH at the PTEN locus is not sufficient to rule out an inactivation of the wild type allele in the tumour cells. Such an inactivation could be the result of another somatic PTEN mutation or a loss of expression by promoter hypermethylation. These hypotheses must be either explored (eventually by screening for allelic exclusion at the RNA level) or discussed.

Minor points:

PHTS not PTHS
oral papillomatous papules
what is QUART? (quadrantectomy?)
Is the IDC ER/PR negative HER2 positive an apocrine carcinoma with AR positive?
SIFT score is 0.01
What is the origin of the XTC UC1 cell line?

**Level of interest:** An article of limited interest

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.